

### **Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

#### **Listing of Claims**

1. (currently amended) A method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, said isolated ligand comprising a heregulin polypeptide selected from the group consisting of heregulin- $\beta$ 2 (SEQ ID NO: 5), heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9), heregulin- $\beta$ 3 (SEQ ID NO: 7), heregulin  $\gamma$  (SEQ ID NO: 11), heregulin- $\alpha$  (SEQ ID NO: 1) variants, heregulin- $\beta$ 1 (SEQ ID NO: 3) variants, heregulin- $\beta$ 2 (SEQ ID NO: 5) variants, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- $\beta$ 3 (SEQ ID NO: 7) variants, heregulin  $\gamma$  (SEQ ID NO: 11) variants, ~~heregulin- $\alpha$  (SEQ ID NO: 1) variants,~~ heregulin- $\beta$ 1 (SEQ ID NO: 3) fragments, heregulin- $\beta$ 2 (SEQ ID NO: 5) fragments, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) fragments, heregulin- $\beta$ 3 (SEQ ID NO: 7) fragments, heregulin  $\gamma$  (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments, wherein

said variants have at least 80% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments comprise ~~amino acids numbered 226 to 266~~ a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

2. (currently amended) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin- $\alpha$  variant, ~~or~~ heregulin agonist antibody ~~or fragment thereof~~ capable of binding to the HER2 or HER3 receptor,

wherein said heregulin- $\alpha$  variant is selected from the group of heregulin- $\alpha$  variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin- $\alpha$  amino acid sequence of SEQ ID NO: 1.

3. (currently amended) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a human heregulin polypeptide or a fragment thereof selected from the group consisting of human heregulin- $\beta$ 2 (SEQ ID NO: 5), human heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9), human heregulin- $\beta$ 3 (SEQ ID NO: 7), human heregulin- $\gamma$  (SEQ ID NO: 11), ~~human heregulin- $\alpha$  (SEQ ID NO: 1) fragments,~~ human heregulin- $\beta$ 1 (SEQ ID NO: 3) fragments, human heregulin- $\beta$ 2 (SEQ ID NO: 5) fragments, human heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) fragments, human heregulin- $\beta$ 3 (SEQ ID NO: 7) fragments, and heregulin  $\gamma$  (SEQ ID NO: 11) fragments.

4. (currently amended) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is selected from the group consisting of ~~heregulin- $\alpha$  (SEQ ID NO: 1) variants,~~ heregulin - $\beta$ 1 (SEQ ID NO: 3) variants, heregulin- $\beta$ 2 (SEQ ID NO: 5), heregulin- $\beta$ 2 (SEQ ID NO: 5) variants, heregulin - $\beta$ 2-like polypeptide (SEQ ID NO: 9), heregulin - $\beta$ 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- $\beta$ 3 (SEQ ID NO: 7), and heregulin - $\beta$ 3 (SEQ ID NO: 7) variants, and fragments thereof, and heregulin- $\alpha$  (SEQ ID NO: 1) variants.

5. (previously presented) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is heregulin- $\gamma$  (SEQ ID NO: 11) or a variant or a fragment thereof.

6. (currently amended) A method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a recombinant human heregulin polypeptide selected from the group consisting of human heregulin- $\beta$ 2 (SEQ ID NO: 5), human heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9), human heregulin- $\beta$ 3 (SEQ ID NO: 7), and human heregulin- $\gamma$  (SEQ ID NO: 11) or a fragment thereof comprising a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

7. (previously presented) The method of claim 1, wherein the supporting cell is in a cochlear implant.

8. (previously presented) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is administered at a daily dose of about 1  $\mu$ g/kg to 100 mg/kg.

9. (currently amended) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin agonist antibody, wherein said heregulin agonist antibody is effective to activate a HER2 or HER3 receptor, and is an antibody raised against a heregulin polypeptide selected from the group consisting of heregulin- $\beta$ 2 (SEQ ID NO: 5), heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9), heregulin- $\beta$ 3 (SEQ ID NO: 7), heregulin  $\gamma$  (SEQ ID NO: 11), heregulin- $\alpha$  (SEQ ID NO: 1) variants, heregulin- $\beta$ 1 (SEQ ID NO: 3) variants, heregulin- $\beta$ 2 (SEQ ID NO: 5) variants, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- $\beta$ 3 (SEQ ID NO: 7) variants, heregulin  $\gamma$  (SEQ ID NO: 11) variants, heregulin- $\alpha$  (SEQ ID NO: 1) fragments, heregulin- $\beta$ 1 (SEQ ID NO: 3) fragments, heregulin- $\beta$ 2 (SEQ ID NO: 5) fragments, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) fragments, heregulin- $\beta$ 3 (SEQ

ID NO: 7) fragments, heregulin  $\gamma$  (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments, wherein

said variants have at least 80% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments comprise a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

10. (original) The method of claim 1, wherein the contacting is by administration to a patient in need thereof.

11. (original) The method of claim 6, wherein the heregulin is rHRG- $\beta$ 1-177-244.

12. (original) The method of claim 1, wherein the inner-ear-supporting cell is in the utricle or cochlea.

13. (canceled)

14. (currently amended) A method of increasing the number of inner-ear-supporting cells, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin- $\beta$ 2 (SEQ ID NO: 5), heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9), heregulin- $\beta$ 3 (SEQ ID NO: 7), heregulin  $\gamma$  (SEQ ID NO: 11), heregulin- $\alpha$  (SEQ ID NO: 1) variants, heregulin- $\beta$ 1 (SEQ ID NO: 3) variants, heregulin- $\beta$ 2 (SEQ ID NO: 5) variants, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- $\beta$ 3 (SEQ ID NO: 7) variants, heregulin  $\gamma$  (SEQ ID NO: 11) variants, ~~heregulin- $\alpha$  (SEQ ID NO: 1) fragments,~~ heregulin- $\beta$ 1 (SEQ ID NO: 3) fragments, heregulin- $\beta$ 2 (SEQ ID NO: 5) fragments, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) fragments, heregulin- $\beta$ 3 (SEQ ID NO: 7) fragments, heregulin  $\gamma$  (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments, wherein

said variants have at least 80% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments comprise amino acids numbered 226 to 266 a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

15. (previously presented) The method of claim 14, wherein the activating ligand is a heregulin- $\alpha$  variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- $\alpha$  variant is selected from the group of heregulin- $\alpha$  variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin- $\alpha$  amino acid sequence of SEQ ID NO: 1.

16. (currently amended) A method of treating a hair cell related hearing disorder, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin- $\beta$ 2 (SEQ ID NO: 5), heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9), heregulin- $\beta$ 3 (SEQ ID NO: 7), heregulin  $\gamma$  (SEQ ID NO: 11), heregulin- $\alpha$  (SEQ ID NO: 1) variants, heregulin- $\beta$ 1 (SEQ ID NO: 3) variants, heregulin- $\beta$ 2 (SEQ ID NO: 5) variants, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- $\beta$ 3 (SEQ ID NO: 7) variants, heregulin  $\gamma$  (SEQ ID NO: 11) variants, heregulin- $\alpha$  (SEQ ID NO: 1) fragments, heregulin- $\beta$ 1 (SEQ ID NO: 3) fragments, heregulin- $\beta$ 2 (SEQ ID NO: 5) fragments, heregulin- $\beta$ 2-like polypeptide (SEQ ID NO: 9) fragments, heregulin- $\beta$ 3 (SEQ ID NO: 7) fragments, heregulin  $\gamma$  (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments, wherein

said variants have at least 80% amino acid sequence identity with the corresponding heregulin sequence, and

said heregulin fragments comprise amino-acids numbered 226 to 266 a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence.

17. (previously presented) The method of claim 16, wherein the activating ligand is a heregulin- $\alpha$  variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- $\alpha$  variant is selected from the group of heregulin- $\alpha$  variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin- $\alpha$  amino acid sequence of SEQ ID NO: 1.

18. (canceled)

19. (currently amended) The method of claim 1, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin- $\beta$  variant, heregulin agonist antibody, or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- $\beta$  variant is selected from the group consisting of heregulin- $\beta$  variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions within SEQ ID NO:3 are at positions S207, H208, L209, V210, K211, E214, E216, K217, T218, V221, N222, G223, G224, E225, M228, V229, K230, D231, N234, P235, S236, R237, Y238,

L239, K241, P243, N244, E245, T247, G248, D249, Q252, N253, Y254, M256, S258, and F259 of SEQ ID NO: 3.

20. (currently amended) The method of claim 14, wherein the activating ligand is a heregulin- $\beta$  variant, heregulin agonist antibody, or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- $\beta$  variant is selected from the group consisting of heregulin- $\beta$  variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions within SEQ ID NO:3 are at positions S207, H208, L209, V210, K211, E214, E216, K217, T218, V221, N222, G223, G224, E225, M228, V229, K230, D231, N234, P235, S236, R237, Y238, L239, K241, P243, N244, E245, T247, G248, D249, Q252, N253, Y254, M256, S258, and F259 of SEQ ID NO: 3.

21. (currently amended) The method of claim 16, wherein the activating ligand is a heregulin- $\beta$  variant, heregulin agonist antibody, or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- $\beta$  variant is selected from the group consisting of heregulin- $\beta$  variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3, wherein the corresponding positions within SEQ ID NO:3 are at positions S207, H208, L209, V210, K211, E214, E216, K217, T218, V221, N222, G223, G224, E225, M228, V229, K230, D231, N234, P235, S236, R237, Y238, L239, K241, P243, N244, E245, T247, G248, D249, Q252, N253, Y254, M256, S258, and F259 of SEQ ID NO: 3.

22. (new) The method of claim 1, wherein the inner-ear-supporting cell is in the cochlea.

23. (new) The method of claim 6, wherein the inner-ear-supporting cell is in the cochlea.

24. (new) The method of claim 11, wherein the inner-ear-supporting cell is in the cochlea.